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10/534,535	09/08/2005	Mara Rossi	272008US0PCT	7168

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
01/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/534,535	ROSSI, MARA	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *4-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/12/2005; 01/08/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

1. Claims 1-9 are pending. Claims 1, 2 and 9 objected to because of the following informalities: the indefinite article "a" should be inserted at the beginning of each of the mentioned claims. Claim 4 is objected to because the units for conductivity (salinity) should be mS/cm and not just mS. Claims 4-9 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 4-9 are withdrawn and have not been further treated on the merits. Claims 1-3 are currently being examined.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolation and preparation of h-TBP-1, does not reasonably provide enablement for all the TNF binding proteins known or to be discovered in the future. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant disclosure fails to meet the enablement requirement for the full scope of the claims for the following reasons:

The meaning of the "TNF-binding proteins" in the instant Application is: "any protein which has an affinity for TNF-alpha or TNF-beta and/or a protein which comprises in the extra-cellular, soluble fragment of a protein belonging to the TNF receptors family, or a fragment thereof" (p. 2, lines 31-34) and is exemplified in the list

spanning page 3, line 1 to page 5, line 16. The list recites a series of proteins that share the common property of binding TNF. The specification however does not present any evidence that the property of the hTBP1 of being able to bind to IMAC and be amenable to purification by the method claimed is linked to its other property of binding TNF. In other words, there is no nexus between the structural feature that allows TNF binding and the property of binding an immobilized metal affinity chromatographic medium containing copper as the metal. The state of the art at the time that the invention was made recognizes the IMAC as a superior way of purifying peptides and proteins (Gaberc-Porekar et al., J. Biochem. Biophys. Meth. 49, 335-360, 2001-cited by the Applicant- p. 336, lines 1-6). However, there are specific requirements for the proteins to be purified by IMAC that need to be fulfilled in order for the process to be successful. The affinity of a protein to an IMAC resin is largely conferred by the availability of the His side chain, imidazole, for interaction with the metal bound to the stationary phase. Other interactions modulate this affinity, like the presence of tryptophan, tyrosine, cysteine, aromatic residues or other histidine in the vicinity of a His that interacts with the immobilized metal. (Wyllie et al., U.S. Pat. No. 5,932,102., col. 1, line 61 to col. 2, line 7). The concept of Solvent-exposed surface area (SESA) of the nitrogen of the imidazole was developed by Wyllie et al. (cited above). Without prediction of the protein-resin affinity, purification development of IMAC based methods may become an unnecessarily time consuming effort which may not yield useful results (Wyllie et al., col.1, lines 50-52). Nevertheless, as late as 2005, it is still considered that, although the retention of peptides is primarily due to the metal affinity of their

individual amino acids, other factors also contribute deeply toward their metal affinity, including amino acid sequences, protein folding, and surface properties. The retention behavior of peptides cannot be easily predicted in IMAC (Chen et al., J Chin. Chem. Soc., 52, 1281-1290, 2005; p. 1282, left col., lines 38-44). The guidance offered in the specification is limited to the actual conditions that were used for the purification of h-TBP-1. The method to be used for the purification of the other TNF binding protein is not detailed, since it is clear from the state of the art that each protein to be purified by IMAC would have its own set of conditions, based at least in part, on the concept of SESA of the imidazole contained in the protein to be purified. This concept is not even addressed in the specification so that the guidance regarding the purification of other TNF-binding proteins is missing; the only working example presented is the one used for the purification of the h-TBP-1.

Due to the large quantity of experimentation necessary to determine the conditions needed for the purification of all the TNF binding proteins; the lack of direction/guidance presented in the specification regarding which structural features are required in order to be considered for a certain method to be successful; the absence of working examples directed to purification of all the TNF binding proteins; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the outcome of the methods in absence of detailed knowledge of protein folding and SESA of the interacting imidazole residues and neighboring residues; and the breadth of the claims which fail to recite any structural or functional limitations, undue

experimentation would be required of the skilled artisan to use the claimed invention in a manner commensurate with its full scope.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaberc-Porekar et al. (J. Biochem. Biophys. Meth. 49, 335-360, 2001-cited by the Applicant) in view of Hauptmann et al. (U.S. Pat. No. 6,271,346) and in further view of Staples et al. (U.S. Pat. No. 5,169,936).

The claims are drawn to a method of isolation and purification of TNF-binding proteins by Immobilized Metal Affinity Chromatography (IMAC) using copper as metal. The elution from the IMAC column is carried out at a pH comprised between 2.8 and 3.2.

Gaberc-Porekar et al. teach that IMAC holds a number of advantages over biospecific affinity chromatographic techniques, which have a similar order of affinity constants and exploit affinities between enzymes and their cofactors or inhibitors, receptors and their ligands or between antigens and antibodies. The benefits of IMAC-ligand stability, high protein loading, mild elution conditions, simple regeneration and low cost- are decisive when developing large-scale purification procedures for industrial applications (p. 336, lines 1-6). The metal used in the metal-chelated affinity support can be Cu (II) (p. 336, last paragraph). Elution of the protein from the column is achieved by protonation with an elution buffer of lower pH and containing between 0.1-1M NaCl (p.337, last paragraph). The authors also teach that, due to the fact that with every IMAC column some leaching of metal ions occurs, in the purification strategy IMAC is usually the first chromatographic step, followed by several polishing steps (p. 352, subheading 7.2). Gaberc-Porekar et al. is silent about the actual pH value for elution and about the purification of a TNF binding protein using their method.

Hauptmann et al. teaches preparation of highly purified TNF-binding protein (TBP-1) from dialyzed urine from uremia patients by a combinations of steps comprising Ion exchange chromatography at a pH 8, affinity chromatography with on a rTNFα Sepharose column eluted with 0.2 M glycine/HCl, pH 2.5, followed by a polishing final step of reverse phase chromatography (Hydrophobic Interaction Chromatography) (Example 1).

Staples et al. teach methods of protein purification using immobilized metal affinity resins containing copper as the immobilized metal (col. 5, lines 24-34). Staples

et al. also teach that a common technique of eluting the proteins adsorbed on an immobilized metal affinity column is to lower the pH to 3 or 4 (col. 1 lines 45-46).

The IMAC offers the benefits underscored by Gaberc-Porekar et al. and the basic steps of the IMAC purification on copper containing resins were iterated by Staples et al. The use of an eluting step with a solution with a pH between 2.8 and 3.2 to ensure a complete removal of the bound TNF binding protein-1 from the copper resin would have been feasible, since Hauptmann et al. proved that hTBP-1 is stable and active even after an elution with a solution of pH 2.5. Therefore, it would have been obvious for a person of ordinary skill in the art at the time that the invention was made to take advantage of the IMAC methods as motivated by Gaberc-Porekar et al. and modify the sequence of purification steps of Hauptmann et al., in view of the teachings of Staples et al. with a reasonable expectation of success.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/

Primary Examiner, Art Unit 1647